New Evidence on Antioxidant Nutrients: Guidelines for Health Education.

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Abstract:
Conflicting information abounds regarding the antioxidant benefits of vitamin C, vitamin E and beta-carotene. In the midst of contradicting information regarding these nutrients, antioxidants (in supplement form) are being aggressively promoted by supplement manufacturers as miracle products for preventing disease and enhancing health. Health educators are sometimes called upon to provide recommendations regarding antioxidant nutrients. This paper discusses some of the accumulating evidence on these nutrients and their antioxidant actions. It also presents information to guide health educators in responding to questions about antioxidants.

Article:
The FDA and the National Academy of Sciences have stated that they do not recommend increases in vitamin C, vitamin E, and beta-carotene in-takes.(1) However, some studies indicate that antioxidant nutrients may lower risks of cancer and heart disease.(2) In addition, antioxidants (in supplement form) are touted by supplement manufacturers as the latest magic bullets for fighting aging and living longer. In the midst of conflicting statements, researchers have attempted to clarify and confirm the roles of antioxidant nutrients in preventing chronic diseases.(2-4)

Health educators are sometimes called upon to provide recommendations regarding antioxidant nutrients. This paper discusses some of the accumulating evidence on nutrients and their antioxidant actions. It also presents information to guide health educators in responding to questions about antioxidants. This information may be useful for health educators working in a variety of situations including clinical settings with patients, behavior change programs, and in teaching institutions during nutrition units of health courses.

Free Radical Formation and the Antioxidant Nutrients
The body's cells use oxygen to produce energy. During these normal metabolic processes, oxygen sometimes reacts with, body compounds to produce unstable molecules known as free radicals -- molecules with unpaired electrons.(2) An unpaired electron is unstable and highly reactive; it needs to pair with another electron in order to return to a stable state. Free radicals quickly react with other compounds in an attempt to capture that needed electron. Antioxidants neutralize free radicals by donating one of their own electrons. (Table 1 defines terms related to antioxidant activity.)

Free radicals not only arise spontaneously during metabolism, but also are made by cells of the immune system to help inactivate viruses and bacteria. In addition to these normal body processes, environmental factors such as radiation, pollution, cigarette smoke, and herbicides can generate free radicals.

TABLE 1
Terms Related to Antioxidant Activity

free radical:	an atom or molecule that has one or more unpaired electron(s) in the outer orbital. This electron imbalance makes free radicals unstable and highly reactive. Radicals typically arise during oxidation reactions and readily attack other molecules with which they come in contact.
nonnutrients:	compounds in foods with no known nutritional value.
oxidant:	a compound (such as oxygen itself) that oxidizes other compounds.
oxidative stress:	damage to biological systems caused by free radical formation.
peroxidation:	the production of unstable molecules containing more than the usual amount of oxygen. Hydrogen peroxide, H_2O_2, for example, may be produced from water, H_2O.
phytochemicals:	naturally occurring chemical compounds other than nutrients found in plants.

The body's natural defense and repair systems attempt to neutralize all free radicals, but they are not completely effective. If antioxidants are unavailable, or if free radical production becomes excessive, problems develop.(5) Free radicals cause damage. They commonly attack lipoproteins and unsaturated fatty acids in cell membranes, starting chain reactions called lipid peroxidation.(6) Left uncontrolled, lipid peroxidation damages cell structures and impairs their functions. Free radicals also damage proteins and DNA.

Rampant free-radical formation and the resulting damage is referred to as oxidative stress. This stress has been implicated in the aging process and in the development of diseases such as cancer, arthritis, cataracts, and heart disease.(7) Researchers have predicted, and to some extent confirmed, that dietary antioxidants help the body fight oxidative stress.(8) Vitamin E, for example, has been credited with reducing the oxidative stresses that accompany diabetes.(9) Daily supplements of vitamin E enhance the action of insulin, it is thought by stabilizing the membranes of responding cells. The result is to improve glucose control in diabetes.(10)

Much research has focused on the theory that antioxidant nutrients act as scavengers of oxygen-derived free radicals, thereby helping to prevent cell and tissue damage that otherwise would give rise to degenerative diseases.(7) The beneficial effects of fruits, vegetables, and grains in fighting degenerative diseases has been attributed, in part, to the antioxidants they provide. The antioxidant roles of several vitamins that are found in these plant foods (beta-carotene, vitamin C, and vitamin E) are under extensive study. For many years scientists believed beta-carotene's sole function was to serve as a vitamin A precursor. Now they recognize that beta-carotene also serves as an antioxidant, important in human health. Vitamin C is the most abundant water-soluble antioxidant in the body and is active primarily in extracellular fluid. Its actions are most notable in combating the free radicals of polluted air and cigarette smoke. Not only does vitamin C neutralize many free radicals, but it helps return vitamin E to its active form. Vitamin E is the most abundant fat-soluble antioxidant and one of the body's primary defenders against oxidation. It protects polyunsaturated fatty acids, all other lipids, and related fat-soluble compounds such as vitamin A.

Vitamin E serves as the body's first line of defense against lipid peroxidation by effectively breaking the chain reaction? In fact, vitamin E is one of the most efficient chain-breaking antioxidants available, reacting 200 times faster than the antioxidant BHT (butylated hydroxytoluene) found in many bakery products. For this reason, a small amount of vitamin E can protect a large amount of lipid.

Antioxidant Nutrients and Cancer

Cancer development occurs when cellular DNA is damaged. Antioxidant nutrients may reduce cancer risks by protecting DNA from this damage. Epidemiological reports indicate a correlation between low intakes of foods rich in antioxidant nutrients and high cancer rates.(11)

Animal studies have shown that beta-carotene protects against cancer.(12) The protective effects vary, depending on the experimental conditions, the types of animals tested, and the cancer types and sites.(13) Research on human beings also produces diverse results. Researchers have compared groups of people that have high cancer rates with groups that have low cancer rates, but that are similar in other characteristics, for example, smoking history and age. They report a consistent relationship between low intakes of vegetables and fruits (specifically of those containing beta-carotene and its relatives) and high rates of lung cancer.(14) Such findings suggest that beta-carotene is protective, but researchers caution the interpretation of such findings; they state that other constituents of fruits and vegetables may be responsible for the effect.(14)

Research has not always made it clear whether preformed vitamin A, beta-carotene, or both are protective against cancer.(15) Some research indicates that dietary vitamin A -- from whatever source -- seems to play a role in inhibiting the development of breast cancer.(16)

Large-scale studies of populations suggest that high vitamin C intake is inversely correlated with rates of certain types of cancer, especially those of the mouth, larynx, and esophagus.(17) Such a correlation may reflect the benefits of a diet rich in fruits and vegetables and low in fat and does not support the taking of vitamin C supplements to treat or prevent cancer.

Some research suggests that vitamin C protects against stomach cancer by preventing the formation of carcinogenic nitrite compounds in the stomach.(18) More research is needed, but the results so far are promising.

Evidence that vitamin E helps guard against cancer is less consistent than for beta-carotene and vitamin C. One large population study showed the highest risks of certain cancers were found in people with the lowest blood levels of vitamin E.(19) The association was strongest for some gastrointestinal cancers and for cancers not related to smoking.

Antioxidants and Heart Disease

Much of the research on antioxidant nutrients has focused on cancer prevention, but antioxidants, especially vitamin E, may protect against cardiovascular diseases as well.(20, 21) Research confirms that high blood cholesterol carried in low-density lipoproteins (LDL) correlates directly with cardiovascular disease. The mechanism by which high levels of LDL cause damage is under study. Some of the most promising research suggests that LDL first undergo oxidation by free radicals inside the artery wall, and then promote the formation of plaques.(22) Evidence thus far is persuasive but not conclusive.(22, 23)

Because oxidized LDL appear to be a factor in heart disease, antioxidant nutrients may be protective against heart disease. Findings from an epidemiological study suggest a negative correlation between vitamin E status and death rates from heart disease.(21, 24) Researchers selected groups of men in 16 European regions where rates of death from heart disease varied sixfold. The researchers measured plasma vitamin E, cholesterol, and blood pressure in men from each region. When the groups were compared, high death rates from heart disease correlated more strongly with low vitamin concentrations than with either cholesterol or blood pressure. The authors cautioned that the evidence for the "antioxidant hypothesis" of heart disease was suggestive, but indirect.(24)

Vitamin C may also affect the susceptibility of LDL to oxidation. Some epidemiological studies have found an association between vitamin C and cardiovascular disease; others have not.(22, 25) Research suggests a synergism between vitamin C and vitamin E in defending LDL against oxidation: Vitamin C, being water-

soluble, defends against free radicals in the fluid compartments of cells and vitamin E, being fat-soluble, acts in lipid environments. Together, they effectively protect LDL against oxidation. In addition, vitamin C may regenerate vitamin E from its oxidized form, making it available to act as antioxidant once again.(26) Some studies also suggest that vitamin C may raise HDL, lower total cholesterol, and improve blood pressure.(25, 27) However, a study in which cholesterol-fed rabbits were fed vitamins E and C produced contrary findings.(28) Although vitamin E and C were shown to inhibit lipoprotein oxidation, they did not reduce the development of atherosclerosis.(28)

Supplements Versus Foods

Some studies suggest that the antioxidant nutrients might help prevent cancer and cardiovascular disease, but these findings are countered by studies that have produced different findings.(29) Although the consumption of fruits and vegetables that contain many antioxidant nutrients has been associated with diminished risks of many cancers, supplements of beta-carotene and vitamins C and E have not always proven beneficial.(11)

For example, a study was conducted to determine whether daily supplements of vitamin E, beta-carotene, or both would reduce the incidence of lung cancer among smokers. After 5 to 8 years of supplementation, there was no reduction in the incidence of lung cancer; in fact, there was a higher incidence of lung cancer in those receiving beta-carotene.(29) Such findings were surprising, especially given the association between high beta-carotene intakes and low rates of lung cancer reported in earlier epidemiological studies. But they highlight the importance of cautious interpretation of limited research findings. They also suggest that remedies to life-threatening diseases such as lung cancer are not as simple as taking daily pills. Smokers are much wiser to stop smoking than to rely on vitamin supplements to protect them from lung cancer.

Antioxidant nutrients behave differently at various levels of intake. At x psychological levels typical of a healthy diet, they act as antioxidants, but at pharmacological doses typical of supplements, they may act as pro-oxidants, stimulating the production of free radicals, especially when metal ions such as iron (also often found in supplements) are present.(30, 32) The FDA and the National Academy of Sciences believe it is premature to recommend increases in vitamin C, vitamin E, and beta-carotene intakes.(1) Government agencies do not support increases in recommendations due to the incomplete nature of antioxidant research.

Another issue of concern when making decisions about recommending supplements to promote health is the potential for vitamin toxicity. Excessive amounts of vitamin E may cause possible GI disturbances and may enhance the anticoagulant effects of drugs, so people on anticoagulant drugs should not take large doses of vitamin E.33 People taking large-dose supplements of vitamin A in its active form risk toxicity. Toxicity symptoms of hypervitaminosis A (vitamin A toxicity disease) are numerous. They include nausea and vomiting; abdominal pain; diarrhea; weight loss; loss of appetite; irritability; fatigue; insomnia; headaches; blurred vision; muscle weakness; amenorrhea; jaundice; enlargement of liver and spleen; massive accumulation of fat and vitamin A in the liver; loss of hemoglobin and potassium by red blood cells; slowed blood clotting time; skin dryness, peeling, and rashes; drying, scaling, cracking and bleeding of lips; nosebleeds; and loss of hair.(34) In addition, vitamin A toxicity causes increased activity of osteoclasts causing decalcification, joint pain, fragility, and stunted growth.(34) Toxicity symptoms of vitamin C include nausea, abdominal cramps, diarrhea, headache, fatigue, insomnia, hot flashes, skin rashes, aggravation of gout symptoms, excessive urination, and formation of kidney stones.(34) Toxicity is a risk when taking supplements, not when consuming a variety of foods.

People taking supplements risk toxicity and the higher the dose, the greater the risk of harm. People's tolerances for high doses of nutrients vary; however, some guidelines have been established for avoiding toxicity. People who do take supplements should not exceed daily doses of 750 retinol equivalents of vitamin A, 30 mg of vitamin E, and 100 mg of vitamin C from supplements.(34)

TABLE 2
Significant Food Sources of Antioxidant Nutrients

Nutrient	Significant Food Sources
Beta-carotene	Spinach and other dark leafy greens; broccoli; deep orange fruits (apricots, cantaloupe) and vegetables (squash, carrots, sweet potatoes, pumpkin)
Vitamin C	Citrus fruits, cabbage-type vegetables, dark green vegetables, cantaloupe, strawberries, peppers, lettuce, tomatoes, potatoes, papayas, mangoes
Vitamin E	Plant oils (margarine, salad dressings, shortenings), green and leafy vegetables, wheat germ, whole-grain products, liver, egg yolks, nuts, seeds

Clinical studies will take several years to complete and until they can prove a clear benefit from taking antioxidant supplements, it would be irresponsible for health care professionals to make such recommendations. The consequences of taking large doses of antioxidants, even naturally occurring ones, over the long term are unknown. Without data to confirm the benefits it would be irresponsible to accept the potential risks that other studies have identified. For as long as the risks of supplement use remain unclear, the best way to supplement antioxidant nutrients is to eat five generous servings of fruits and vegetables daily, especially citrus fruits and green and yellow vegetables. Table 2 lists significant food sources of each antioxidant vitamin.

The Food and Drug Administration (FDA) examined the available scientific evidence concerning antioxidant vitamins and cancer to determine whether a health claim on food labels was appropriate. The FDA concluded that diets high in fruits and vegetables, which are good sources of two antioxidant vitamins (beta-carotene and vitamin C), are strongly associated with reduced risks of several types of cancer.(35) Still, the FDA rejected the antioxidant health claim, stating that the reduction in risk could not be attributed directly and solely to the antioxidant effect of the vitamins.(35) Therefore, labels may not claim an association between antioxidant vitamins and cancer; the health claim must be stated in terms of fruits and vegetables and cancer.

Foods deliver thousands of chemicals other than nutrients. For this reason, researchers must be careful in giving credit for particular health benefits to any one nutrient.(36) Diets rich in whole grains, legumes, vegetables, and fruits seem to be protective against cancer, but identifying the responsible foods or components of foods specifically is difficult. Green leafy vegetables such as spinach and kale, for example, contain lutein, an antioxidant more active than beta-carotene. The anticancer benefits of green leafy vegetables may be due to beta-carotene, but they may be due to lutein -- or to another as yet unnamed compound. Perhaps credit even belongs to the unique combination of chemicals found in leafy greens.

The identity and action of every chemical in every' food is unknown. Even if this complete knowledge were available, selecting a supplement to replicate a food deprives one of the pleasure, nourishments, and health benefits that only foods can provide. Single nutrients should not take the place of a healthy diet and lifestyle. Instead, people are wise to eat a wide variety of fruits and vegetables in generous quantities every day -- and obtain all the health benefits these foods have to offer.

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